UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,748	03/30/2005	Berislav V Zlokovic	GRT/4061-32	1588

23117 7590 08/07/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
08/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,748	ZLOKOVIC ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11,13,16-18 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-11,13,16-18 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks, amendments, and declaration filed 21 April 2008 have been entered. Claims 1 – 5, 12, 14 – 15, and 19 – 24 are canceled; claims 25 – 34 are new. Claims 6 – 11, 13, 16 – 18, and 25 – 34 are pending and under examination.

Withdrawn Rejections

2. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 102(a) over Cheng is withdrawn in light of the declaration filed under 37 CFR 1.132. The declaration under 37 CFR 1.132 filed 21 April 2008 is sufficient to overcome the rejection of claims 6 – 18 based upon anticipation. The declaration provides evidence that all authors listed on the Cheng publication who are not also inventors of this application did not make an inventive contribution; see particularly paragraphs 6 – 9 of the declaration. Therefore the reference by Cheng is not "by another" and does not qualify as prior art under 35 USC 102(a).

B. The rejection under 35 USC 102(b) over Schwarz is withdrawn. While Schwarz teaches administration of protein S for protection against trauma, and the reference also claims treatment of patients with thromboembolic complications (see claim 1), Schwarz does not explicitly teach administration to human patients with the conditions recited in independent claims 6, 25, and 30.

C. The rejection under 35 USC 102(e) over Hung is withdrawn. Although Hung teaches administration of protein S (see for example paragraph [0041]), including human form of the protein (see paragraph [0085]) for treatment of diseases including ischemic syndromes, the reference does not explicitly teach administration to a human patient as recited in independent claims 6, 25, and 30.

D. The double-patenting rejection is withdrawn in light of the amendments to the claims. The claims all now require that no protein C or activate protein C be administered. All the claims of U.S. 7,074,402 require that activated protein C be administered; and therefore the instant claims are not an obvious variant of the previously-issued claims.

Maintained Rejections

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8 – 11, 13, 16 – 18, 25, 27 – 30, and 32 – 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of human protein S, does not reasonably provide enablement for administration of the full scope of variants at least 95% identical to same which have the properties recited in claims 8 – 11, 27 – 28, and 32 – 34. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons previously made of record and explained in further detail below. While the claims are drawn to methods of administering protein S variants, what is not enabled by the specification is that products which are required for the methods. Thus discussion here focuses on the products. The independent claims encompass administration of variants at least 95% identical to human protein S. Dependent claims 8 – 11, 27 – 28, and 32 – 33 recite certain properties which the variants are required to have. The specification does not disclose to the skilled artisan which residues can be varied such that these properties are retained. While it is within the skill of the artisan to make variants, there is no guidance as to which residues, either on their own or by virtue of interaction with other amino acids, impart the recited properties to the variants. There is no guidance as to which regions of protein S should be retained, and there is no guidance as to which regions can be varied. There are no working examples of variants which are 95% (or greater) identical to human protein S and which either have or do not have the recited properties. Thus the skilled artisan would have to determine, on his or her own, which regions of the large protein (protein S is over 600 amino acids) should be varied. The art of record (Rudinger, Honig, both cited in previous office action) indicates that predicting protein function from structure is very difficult. Therefore, the large degree of experimentation required for the skilled artisan to make the full scope of products recited in claims 8 – 11, 27 – 28, and 32 – 33 would be undue. Claims 6, 25, and 30 are included in this rejection as these are independent claims which encompass these

dependent claims as well. Claims 13, 16 – 18, 29, and 34 are included in this rejection as they depend from a rejected base or intermediate claim. Note claims 7, 26, and 31 are not included in this rejection as they are drawn to administration of "human protein S" and clearly do not encompass administration of the variants.

On pp. 5 – 6 of the remarks filed 21 April 2008, applicant argues that pp. 12 – 17 of the specification provide sufficient guidance to the skilled artisan to make all products encompassed by the rejected claims. Applicant's arguments have been fully considered but they are not persuasive. While the cited text discusses certain properties of protein S, and indicates that certain variants were known, there is no disclosure as to whether the variants change any of the properties recited in the instant claims. That is, the specification fails to provide guidance to a skilled artisan to indicate which structural elements are responsible for the recited properties. Given as there is not sufficient guidance, the artisan would have to resort to random mutations throughout the 600-plus amino acid sequence in order to discover which structural elements lead to the functions recited. Therefore, the degree of experimentation required would be undue. The rejection stands.

4. Claims 6, 8 – 11, 13, 16 – 18, 25, 27 – 30, and 32 – 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection stands for the reasons previously made of record and explained in further detail below. Briefly, the claims are drawn to methods of administering protein S variants, including those variants at least 95% identical to human protein S which have certain function. The specification fails to describe which sequences within human protein S impart the functions recited in claims 8 – 11, 27 – 28, and 32 – 33. The skilled artisan cannot envision the structure of the genus of products which are to be administered in the claims.

Applicant states, on p. 6 of the remarks, that there is sufficient correlation between structure and function to meet the written description requirement. The examiner has closely studied the cited pages of the specification but has not been able to find disclosure of the sequences which are either necessary or sufficient to provide the recited properties to the

variants of human protein S which are 95% identical to that sequence. Applicant is directed to the newly-revised written description guidelines, available on the internet at http://www.uspto.gov/web/menu/written.pdf. Example 11, drawn to variants of proteins when a correlation between the structure and a specific function recited in a claim is particularly on point to the instant fact pattern.

Claims 6, 25, and 30 are included in this rejection as these are independent claims which encompass the dependent claims that recite the specific properties. Claims 13, 16 – 18, 29, and 34 are included in this rejection as they depend from a rejected base or intermediate claim. Note claims 7, 26, and 31 are not included in this rejection as they are drawn to administration of "human protein S" and clearly do not encompass administration of the variants.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8 – 11, 13, 16 – 18, 25, 27 - 30, and 32 - 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 6, 25, and 30 are each indefinite because the allow for up to 5% variation from an unspecified sequence. Protein S is not a single sequence, but can exist in multiple forms. For example, Bouma (U.S. Patent 5,663,142, of record) teaches that Protein S has a signal sequence, which is cleaved during intracellular processing (see column 5 lines 40 – 44). Additionally protein S has a propeptide (specification, p. 12). It is unclear whether applicant considers the signal sequence and propeptide to be part of “human protein S” as recited in claims 6, 25, and 30. Furthermore, it is unclear whether the signal sequence should be included when one calculates identity between two sequences. That is, the skilled artisan could not determine whether any given sequence is greater than 95% identical to human protein S, since it is unclear what sequence should be used for comparison. Thus the independent claims are unclear. Claims 8 - 11, 13, 16 - 18, 25, 27 - 29, and 32 - 34 are included in this rejection as they depend from a rejected base or intermediate claim but do not further clarify the

ambiguity. Note claims 7, 26, and 31 are not included in this rejection as they are drawn to administration of "human protein S". While there are multiple forms of human protein S as described above, this fact indicates that claims 7, 26, and 31 are broad but are not necessarily indefinite.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6 – 11, 13, and 16 – 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bouma (U.S. Patent 5,663,142, issued 2 September 1997, cited on IDS filed 27 April 2005).

Bouma teaches administration of protein S variants at least 95% identical to human protein S. The protein S variants, which are within the scope of instant claim 6, are to be administered to human patients suffering from thrombosis, a condition in which a clot forms, occluding blood flow, and necessarily resulting in ischemia. See Bouma's claim 8, note patients with thrombosis are listed separately from those with protein S deficiency. The reference anticipates every element of claim 6. Claims 8 – 11 and 16 - 18 are included in this rejection as the prior art product is presumed to have the recited properties and effects, absent evidence to the contrary. Reliance on the doctrine of inherency is appropriate when a prior art reference teaches the same product or method of using a product, but is silent as to properties of the products; see MPEP § 2112(III).Claim 7 is included as Bouma teaches administration of human protein S. Claim 13 is anticipated as the patients are not disclosed as having protein S deficiency.

7. Claims 6, 8 – 11, 13, 16 – 18, 25, 27 – 30, and 32 – 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Bertilsson (U.S. Patent Application Publication 2003/0165485, published 4 September 2003, filed 8 November 2002, claiming benefit of provisional applications filed 9 November 2001 and 8 July 2002).

Berilsson teaches methods of treating neurological diseases comprising administering protein S. See for example paragraphs [0016] and [0051], as well as claim 32. The diseases to be treated include cerebral ischemia, stroke, and neurotrauma; see paragraph [0139]. Berlisson specifically teaches that humans are to be treated; see paragraph [0140]. Thus the reference anticipates independent claims 6, 25, and 30.

Claims 8 – 11, 17 – 18, 27 – 28, and 32 – 33 are included in this rejection as the protein S necessarily has the recited properties and administration will lead to the effects recited in claims 17 – 18. Claims 13, 29, and 34 are anticipated as the patients are not disclosed as having any protein S deficiency. Claim 16 is anticipated as the protein S can be administered after diagnosis of stroke; see paragraph [0016] and claim 32 which indicate that patients suffering from disease are those to be treated.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6 – 11, 13, and 16 – 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (U.S. Patent Application Publication 2003/0060415, published 27

March 2003, filed 2 October 2002, claiming benefit of earlier-filed applications from 1 November 1996 and 1 November 1995).

Hung teaches administration of compositions comprising protein S for treatment and prevention of many conditions including ischemia and reperfusion injury, recited in claim 6. See Hung, paragraph [0011] and [0019] – [0039] for diseases to be treated or prevented; see also paragraph [0041] as well as claims 1 and 48 which specifically list protein S as an agent to be administered for such treatment. Note claim 6 does not require that the patient be suffering from cerebral ischemia, hypoxia, or repurfusion; the claim is sufficiently broad to encompass other forms of damage (e.g. coronary ischemia). Additionally, Hung teaches that protein C and activated protein C can be omitted; note that their inclusion is optional (see for example claim 48, which lists protein C as a separate alternative to be administered). Hung teaches that the human form of the protein should be used (see paragraph [0085]), which is on point to claim 7. Absent evidence to the contrary, the human form of the protein is presumed to have the properties recited in claims 8 – 11. The subjects to be treated are not disclosed as having protein S deficiency, which is on point to claim 13. The treatment is to occur before diagnosis of some future condition, which is on point to claim 16. The administration of protein S will necessarily result in increase in cerebral blood flow, which is on point to claim 17, and change in brain volume, which is on point to claim 18. Note claim 18 does not require that the patient have cerebral ischemia, but recites effects which will happen following administration of the protein. However while Hung teaches treatment of patients in general, the reference does not explicitly teach treatment of human patients, as recited in claim 6.

Nonetheless, it would have been obvious to one of ordinary skill in the art to select humans for treatment, as opposed to some other species. The reference by Hung specifically directs the artisan of ordinary skill to select human proteins for administration (paragraph [0085]), suggesting that humans should be treated. Additionally, the artisan of ordinary skill would be motivated to treat human disease.

9. Claims 6 – 11, 13, 16 – 18, and 25 – 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bertilsson (U.S. Patent Application Publication 2003/0165485, cited above) in view of Hung (U.S. Patent Application Publication 2003/0060415, of record).

The reasons why Bertilsson anticipates claims 6, 8 – 11, 13, 16 – 18, 25, 27 – 30, and 32 – 34 are set forth in the rejection under 35 USC 102 above and for the sake of brevity will not

be repeated here. While Bertilsson teaches administration of Protein S to humans suffering from stroke, ischemia, and neurotrauma for treatment of such conditions, the reference does not explicitly teach administration of human protein S, as recited in claims 7, 26, and 31.

The teachings of Hung are set forth in the rejection under 35 USC 103(a) above. Briefly, Hung teaches administration of compositions comprising protein S for treatment and prevention of many conditions including ischemia and reperfusion injury, recited in claim 6. Hung teaches that the human form of the protein should be used (see paragraph [0085]), which is on point to claims 7, 26, and 31. However Hung does not explicitly teach administration of protein S for treatment of neurotrauma or stroke, as recited in independent claims 25 and 30.

It would have been obvious to one of ordinary skill in the art to select the human protein S taught by Hung, for use in the methods taught by Bertilsson, thereby arriving at the specific methods recited in claims 7, 26, and 31. The motivation to do so would be to minimize the adverse immune responses that frequently occur upon administration of foreign proteins. By selecting the human protein S, taught by Hung, for administration to humans, the artisan of ordinary skill would be able to minimize adverse complications in the therapeutic methods taught by Bertilsson.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
August 3, 2008